

Appl. No. 09/996,657
 Atty. Docket No. 8375D
 Amdt. Dated: July 11, 2003
 Reply to Office Action of: February 11, 2003
 Customer No. 27752

REMARKS

Claims 17 - 26 are pending in the present application. No additional claims fee is believed to be due. Claims 17 and 23 have been amended to delete the term "about" from the claims.

The Rejection Under 35 USC § 112, Second Paragraph

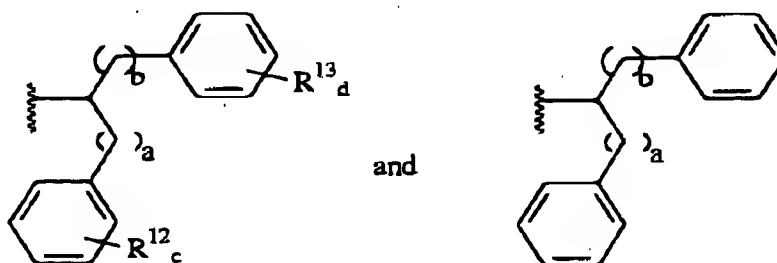
The Examiner has rejected Claims 17 and 23 under 35 USC § 112, second paragraph as being indefinite. Applicants have herein amended Claims 17 and 23, deleting the term "about" from the claims and thereby deleting the portion of the claims that Examiner has found to be fractional. The term "about" has been deleted from the indicated sections a), b), c), d), and element "i" in Claim 17 and has also been deleted from dependent Claim 23. Applicant respectfully asserts that these amendments overcome the Examiner's rejection of Claim 17 and 23 under 35 USC § 112, second paragraph and that the rejection should be promptly withdrawn.

The Rejection Under 35 USC § 102

The Examiner has rejected Claims 17, 19, 22, 23, 24 and 25 as anticipated by compounds disclosed in DE 3524955 and FR 2567885 (which appear to be the same reference).

The Examiner states that Compound 56 of the cited reference discloses a compound that can be in structure similar to a compound represented in Applicants' claims, wherein x is 0, D^1 is NH, D^2 is C=O, R^2 is a biphenyl of the group as given in Claim 6, R^1 is hydrogen, or hydroxy, D^4 is CHR^1 , t is 2, D^5 is OR^6 , and R^6 is a substituted hydrocarbon group, or a substituted aromatic group according to the definitions given in the specifications.

Applicant respectfully traverses the Examiner's rejection. As amended herein, independent Claim 17 requires that each R^2 is selected from:



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wherein *a* is at least 2 and *b* is at least 2. Accordingly, R^2 cannot be a diphenylmethyl group as exemplified in the cited reference. Therefore, the present claims are not anticipated by the Compound 56 of the cited reference, and the rejection should be withdrawn.

Moreover, contrary to the Examiner's implication, the claimed invention would not have been obvious in view of Compound 56 as cited by the Examiner. Courts have challenged obviousness rejections under 35 USC § 103 based on structural obviousness by finding that new and unexpected properties of compounds are indicative of the non-obviousness of the claimed invention. See e.g., Warner-Jenkinson Company v. Allied Chemical Corporation, 477 F. Supp. 371 (U.S. Dist. 1979); Commissioner of Patents v. Deutsche Gold-und-Silber, 397 F.2d 656 (D.C. Cir. 1968); In re Papesch, 315 F.2d 381 (CCPA 1963). The Examiner is compelled to follow these rules of law, particularly in view of the following comparison of the properties of the cited Compound 56 (as disclosed) and Applicants' compounds (as newly discovered):

Properties described by DE3524955 and FR 2567885 (believed to be the same reference)

The cited reference describes compounds that possess cardiologic activity. The reference describes that, in trials, administration of the compounds intravenously to an animal resulted in increased heart rate. The compounds are therefore further described in the cited reference as being useful for the treatment of heart insufficiency. The referenced disclosure also indicates that the compounds can be used for the treatment of heart rhythm disorders such as supraventricular tachycardia or fibrillation.

The compounds of the cited reference are also described for use as α -adrenoceptor and β -adrenoceptor blocking agents. Therefore, included in the utility of the claimed compounds is treatment of disorders relating to intestinal motility and for the treatment of coronary disease such as angina pectoris, of conditions from sympathetic overstimulations, such as nervous heart ailment, of hypertension, of myocardial infarct, for interval migraine treatment, and for the treatment of glaucoma, and for thyrotoxicosis.

Finally, the compounds of the cited reference are described as exhibiting effects typical of calcium antagonists. They are described as exhibiting muscle-relaxant activity, particularly in smooth muscle as exhibited by vasodilation and blood pressure lowering.

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The cited reference is therefore limited to teaching those of ordinary skill in the art that the compounds described therein, including Compound 56, are useful for certain described ailments of the heart.

The Present Invention

Applicants have discovered that the presently claimed compounds, and compositions incorporating such compounds, are useful for treating multidrug resistance. Multidrug resistance is a circumstance whereby a system does not respond to a variety of therapeutic agents that may be functionally unrelated, structurally unrelated, or both. Examples of properties exhibited by Applicants' compounds include treatment of cancer by blockage of pleiotropic-glycoproteins which are found in high quantities in cancer cells, and blockage of MRP1-mediated multidrug resistance. Blockage of the pleiotropic-glycoproteins by the compounds claimed by Applicants, for instance, inhibits these glycoproteins from exporting hydrophobic compounds out of a cell that are useful for treating cancer. Related activity includes prevention of multidrug resistance to antibacterial, antiviral, and antifungal compounds. A further utility of the compounds and compositions of the present invention is inhibition of pleiotropic-glycoproteins in areas where high levels of the protein are found, including the gastrointestinal tract, liver, kidneys, and brain; thereby helping many areas of the body to defend against the formation of cancer. While the claimed compounds and composition may be utilized with other uses, potentially including uses for cardiac treatment, the discoveries made by Applicants herein are unique.

Applicable Case Law

In a leading case relating to compounds found to be structurally obvious by the Examiner, *In Re Papesch*, 315 F.2d 381 (CCPA 1963), the United States Court of Customs and Patent Appeals reversed the Board's rejection of appellant's patent application for a compound structure, wherein the Board had found that ethyl and n-butyl side chains depicted in appellant's claims were obvious homologs of the methyl groups shown in identical positions in prior art compounds. The Court of Customs and Patent Appeals overruled the Board, finding that the compounds claimed by appellant possessed anti-inflammatory activity, an unobvious and unexpected beneficial property not possessed by the homologous compounds disclosed in the prior art. The Court of Customs and Patent Appeals held that a compound structurally similar to a prior art compound may nevertheless be non-obvious and patentable when it possesses unexpected properties.

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In addition, in *Warner-Jenkinson Company v. Allied Chemical Corporation*, 477 F. Supp. 371 (U.S. Dist. 1979), the test for obviousness of a chemical compound was described as follows:

Because the enormous number of known organic compounds gives rise to a situation in which absolutely unique and unknown groupings of atoms in a completely new chemical compound is a rare occurrence, courts have generally held that such compounds are patentable even though similar compounds or isomers are well-known in the field. Obvious molecular modification coupled with a showing of novel properties or superiority over known properties can establish patentability. Since Judge Rich's celebrated decision in *In re Papesch*, courts have been moving to a test of "essential predictability," balancing the significance of unexpected properties resulting from minor chemical manipulations of existing compounds against the desirable properties that would be expected from such alterations.

The test of "essential predictability" has been developed primarily in the Court of Customs & Patent Appeals. See e.g., *In re May*, 574 F.2d 1082, 1092, (CCPA 1978); *In re Wilder*, 563 F.2d 457, 460 (CCPA 1977); *In re Albrecht*, 514 F.2d 1389 (CCPA 1975); *In re Hoch*, 428 F.2d 1341, (CCPA 1970).

Citing the above precedent, and very similar to the facts of *In re Papesch*, are the facts of this related to the present invention. The Examiner has stated that, for one embodiment of the present invention, it is possible for the chemical structure to differ by just two methyl groups from that of Compound 56 in the cited reference. However, respectfully, the Examiner appears to have overlooked the unexpected properties exhibited by the compounds of the present invention (multidrug resistance) relative to the properties disclosed in the cited reference (cardiologic activity). While this does not preclude use of the present compounds and compositions in the treatment of conditions of the heart, these newly discovered properties with respect to multidrug resistance results in a patentable and non-obvious invention that is "essentially unpredictable" relative to the cited reference.

Obviousness results under 35 U.S.C. § 103 when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time of the invention to a person having ordinary skill in the art. Based on the foregoing, the present invention would not have been obvious to one skilled in the art because the compounds, and compositions containing such compounds, are useful for a benefit which would not have been expected in view of the cited reference. For the aforementioned reasons,

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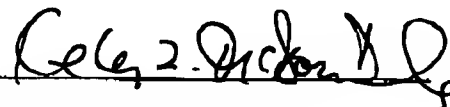
Applicants therefore respectfully assert that the claimed invention would not have been obvious in view of the cited reference.

CONCLUSION

Applicants have made an earnest effort to place the present application in allowable form and to distinguish the invention as now claimed from the cited reference. In light of the above remarks, it is respectfully requested that the Examiner reconsider and withdraw the rejections under 35 USC §§ 112, 102 and 103. As such, in view of the foregoing, Applicants respectfully request reconsideration of this application, entry of the amendments presented herein, and allowance of Claims 17 - 26.

Respectfully submitted,

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